a label wherein the label is a lanthanide ion-ligand complex formed by contacting a lanthanide ion and a ligand, wherein the lanthanide ion is selected from the group consisting of neodymium (III) ion (Nd^{3+}), ytterbium (III) ion (Yb^{3+}), and erbium (III) ion (Er^{3+}), and wherein the ligand is in contact with a sensitizing moiety which absorbs light in the 400-1000 nm region.

13. (Amended) The kit as claimed in claim 5, wherein the specific binding partner and the reactant or immunoreactant are attached to a carrier.

14. (Amended) The kit as claimed in claim 12, wherein the specific binding partner and the reactant or immunoreactant are attached to a carrier.

REMARKS

This preliminary amendment accompanies the Continued Prosecution Application filed herewith and is also a response to the Final Rejection dated August 14, 2001 in the above-identified application.

Claims 1, 4-6, 8-10, and 12-14 have been amended. Claims 1-14 are currently pending in the present application. Applicant filed an amendment after final on November 14, 2002 in response to the Final Rejection dated August 14, 2001. The amendment after final filed on November 14, 2002 was not entered by the Examiner as indicated in the Advisory Action dated February 4, 2002.

In claims 1, 5, 10 and 12-14, "immunoreactant" has been amended to "reactant or immunoreactant" for the following reasons. In the original claims, the term employed was (immuno)reactant. The parentheses in such a term are used to abbreviate two different materials

as is the common practice in chemistry. For example, the phrase (immuno)reactant means both reactant and immunoreactant. Because the original claims 1 and 5, from which the amended claims 1, 5, 10 and 12-14 are derived, recites "(immuno)reactant, claims 1, 5, 10 and 12-14 have been amended accordingly to remove the parentheses as requested by the Examiner and have been rewritten in longhand form to include both possibilities in order to retain the meaning and scope of the original claims.

Claims 1-4, 6 and 8-14 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite. The specific detailed rejections are addressed below.

In claim 1, line 11, Applicant has changed "luminance" to "luminescence" in order to correct the misspelling.

Claims 1 and 10 have been rejected as incomplete for omitting a detection step. Claims 1 and 10 have been amended in order to further require the step of: "detecting the analyte using said luminescence measurement." It is considered that this amendment overcomes the rejection of claims 1 and 10.

Claim 4 was rejected as indefinite for reciting "complexing ability" in line 4 of the claim. Claim 4 has been amended to require that the various moieties can complex with the various ions recited in the claim. It is considered that this amendment renders claim 4 definite since a skilled person can run a simple test to determine whether a particular moiety can complex with a particular ion and therefore can routinely determine the scope of the present claim 4, as amended. Accordingly, favorable consideration and withdrawal of the rejection of claim 4 in view of the amendment is requested.

Claims 6 and 9 have been rejected on the basis that they require that the detector be "capable of detecting" luminescence in a particular wavelength range. Claims 6 and 9 have been

amended to require a detector which detects luminescence in a particular wavelength range. It is considered that this amendment overcomes the rejection. More specifically, a skilled person can, using a routine test, determine whether a particular detector detects luminescence in a particular wavelength range. Thus, it is a routine matter for a skilled person to determine whether a particular detector meets this limitation of the claim. For this reason the claims 6 and 9 are definite. Favorable consideration and withdrawal of the rejection is requested.

Claim 10 has been rejected on the basis that luminescence is misspelled in line 11. The spelling error has been corrected. In addition, claim 10 has been rejected as vague and indefinite in reciting "in contact" because it is unclear and fails to specifically define what is encompassed by the term "contact." This rejection is respectfully traversed and reconsideration is requested. More specifically, this limitation is explained on page 3, lines 1-4 of the specification. It is a routine matter for a skilled person to determine if a sensitizer is in contact with a ligand based on this definition given in the disclosure. Accordingly, since it is a routine matter to determine the metes and bounds of claim 10, claim 10 is considered to be sufficiently definite to meet the requirements of 35 U.S.C. §112. Favorable consideration and withdrawal of the rejection is requested.

Claim 12 was rejected for the same reason as claim 10, namely that it employed the terminology "in contact". The same argument applies to claim 12. Favorable consideration and withdrawal of the rejection is requested.

Claims 13-14 have been rejected as vague and indefinite in reciting the term "attached." This rejection is respectfully traversed and reconsideration is requested for the reasons which follow.

More specifically, it is submitted that the term "attached" is sufficiently definite for a person of ordinary skill in the art to be able to routinely determine whether a particular specific binding partner, or a reactant or immunoreactant is attached to a carrier by applying a simple test. The term "attached" should be given its common meaning to a person of ordinary skill in the art. For example, "attached" is clearly explained in the specification on page 9, lines 5-10. The specification also gives details regarding examples of attachments in this paragraph. Accordingly, in view of these facts, it is submitted that "attached" is sufficiently definite such that a skilled person can determine the scope of claims 13-14. For these reasons, withdrawal of the rejection of the claims 13-14 is requested.

Claims 13-14 have been rejected on the basis that it is unclear whether the "the specific binding partner" and the "reactant or immunoreactant" are each attached to the same carrier or each attached to a separate carrier. Claims 13-14 only require that the specific binding partner, and reactant or immunoreactant be attached to a carrier. The way the claims read now the claims encompass either the situation where both the specific binding partner, and the reactant or immunoreactant are attached to the same carrier, or the situation where the specific binding partner, and the reactant or immunoreactant are attached to two different carriers. This does not render the scope of claims 13-14 indefinite since a person with skill in the art can determine whether the specific binding partner, or the reactant or immunoreactant are attached to a carrier and therefore can determine the metes and bounds of claims 13-14. Accordingly, favorable consideration and withdrawal of the rejection of claims 13-14 is requested for these reasons.

In addition, in the Advisory Action dated February 4, 2002, the Examiner stated: "claim 1 fails to set forth what interaction, i.e., binding to form a ternary complex, takes place so as to effect luminescence in the mixture and how luminescence relates to the detection of the analyte,

i.e., luminescence detected is indicative of the presence of analyte in the sample." Therefore, claim 1 was still considered indefinite. Applicant disagrees and submits that amended claim 1 is definite for the reasons below.

First, there is nothing indefinite about claim 1. Claim 1 clearly recites every single step required to carry out the invention. With regards to the "interaction" suggested by the Examiner, it may be inherent to the method or it may not be inherent to the method. In fact, the interactions between all the ingredients used in the method do not have to be understood or set forth in the claims in order to for the method to be practiced. For example, a user of the present invention can simply rely on an empirical calibration of the detector to determine the amount or the presence of a particular analyte without understanding how the luminescence spectrum is generated by the lanthanide-ligand complex employed in the present invention. Furthermore, the lack of explanation of the interaction between the ingredients employed by the present invention has nothing to do with indefiniteness. A person skilled in the art can easily determine if a method involves the steps recited in claim 1, and thus can determine if a particular method falls within claim 1. Therefore, claim 1 is definite.

Finally, Applicant wants to point the Examiner's attention to MPEP §2173.04, which is quoted as below:

> Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear; and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.

Accordingly, Applicant respectfully submits that claim 1 is definite and withdrawal of the rejection is respectfully requested.

Claims 1-14 have been rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,159,686 (Kardos et al.). This rejection, at least insofar as it applies to claims 1-14, as amended, is respectfully traversed and reconsideration is requested for the reasons which follow.

Claims 1-14, as amended, relate to the methods and apparatus for detection of an analyte in a test sample. In the method, a lanthanide ion-ligand complex is prepared by contacting a lanthanide ion and a ligand comprising, or in contact with, a sensitizing moiety which absorbs light in the 400-1000 nanometer region. A reactant or immunoreactant is labeled with the lanthanide ion-ligand complex by contacting the reactant or immunoreactant with the lanthanide ion-ligand complex to form a labeled reactant or immunoreactant. An analyte, a specific binding partner for the analyte and a labeled immunoreactant are mixed to form a mixture and the mixture is irradiated with light having a wavelength ranging from 400 nanometers to 1000 nanometers. Finally, the emitted luminescence of the mixture is measured and an analyte is detected using the luminescence measurement.

The present invention comprises a specific binding partner for the analyte, a reactant or immunoreactant and a label which is a lanthanide ion-ligand complex, wherein the ligand comprises, or is in contact with, a sensitizing moiety which absorbs light in the 400-1000 nanometer range so that the light energy absorbed by the sensitizing moiety can be transferred to the lanthanide metal that the ligand binds to. The present invention also includes an apparatus for detection of an analyte comprising the kit as claimed, a light source for emitting a single photon in the 400-1000 nanometer range and a detector which can detect luminescence in the 800-1600 nanometer range.

In contrast, Kardos et al. teaches a photoluminescence assay using a less efficient two-photon excitation process. In this assay, a probe such as an antibody is labeled with an up-converting reporter such as an inorganic or organic up-converting fluorescence emitting material. The probe is then contacted with particular analytes followed by exciting the up-converting fluorescence emitting material with an intense near-IR light source. The excited up-converting fluorescence emitting material then emits an output emission in the visible wavelength region and thereby returns to the ground state. A detector detects the emission in the visible light wavelength and determines whether particular analytes are present.

To further support Applicant's position, Applicant encloses herewith a declaration of Dr. Clemens Brunner, an expert in the area of photoluminescence. As pointed out by Dr. Brunner in his declaration at paragraph 10, the up-converting fluorescence emitting material used in Kardos et al. can be categorized into two categories: inorganic up-converting fluorescence emitting materials and organic up-converting fluorescence emitting materials. Exemplary inorganic up-converting fluorescence emitting materials are $Na(Y_xYb_yEr_z)F_4$ (cols. 15 and 16 of Kardos et al.), which is a lanthanide-containing material. Exemplary organic up-converting fluorescence emitting materials are rhodamines (col. 30, lines 44-46). The assay of Kardos et al. generally employs one of these up-converting fluorescence emitting materials. The inorganic fluorescence emitting materials such as those containing lanthanide are generally heterogeneous particles (see col. 17, lines 23 – 41 of Kardos et al.). The inorganic fluorescence emitting materials do not include a ligand containing a sensitizing moiety absorbing light in the 400-1000 nm region. The organic fluorescence emitting materials employed by Kardos et al. do not include a lanthanide metal ion.

Even though it is possible to use both the organic and inorganic fluorescence emitting materials in one assay (see col. 12, lines 60-62 of Kardos et al.), using two fluorescence emitting materials does not provide any additional benefit to the assay. Should an organic up-converting fluorescence-emitting material be used together with an inorganic up-converting fluorescence-emitting material, these two materials would function independently. The lanthanide fluorescence emitting material and the organic fluorescence emitting material disclosed in Kardos et al. will not form a complex (in contrast to the complex formation requirement of the present invention) when they are combined in a mixture because the lanthanide contained in the inorganic up-converting fluorescence emitting material is heterogeneous and is therefore incapable of binding to another ligand to form a complex. In addition, using more than one up-converting fluorescence emitting material in one assay will complicate the emission spectrum of the assay and make the analysis more difficult because each up-converting fluorescence emitting material in the assay will emit its own emission.

Unlike Kardos et al., the present invention employs a ligand comprising a sensitizing moiety or inherently in contact with the ligand. Therefore, after formation of the lanthanide-ligand complex, the sensitizing moiety is also in direct contact with or is a part of the lanthanide-ligand complex. This close relationship between the sensitizing moiety and the lanthanide-ligand complex allows the sensitizing moiety to transfer its absorbed light energy to the lanthanide metal in the lanthanide-ligand complex.

In addition, Dr. Brunner further points out clearly at paragraphs 10 and 12 of his declaration that Kardos, et al. teaches a two-photon process which operates via a substantially different pathway and employs a substantially different lanthanide containing material. Dr. Brunner further points out that Kardos does not employ a ligand-lanthanide complex, wherein

the ligand contains a sensitizing moiety that absorbs light in the 400-1000 nm range (see paragraph 17 of the declaration). Favorable consideration and withdrawal of the rejection under 35 U.S.C. §102(e) is requested.

Claims 1-14 have been rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,830,769 (Wieder, et al.) in view of Kardos, et al. This rejection, at least insofar as it applies to claims 1-14, as amended, is respectfully traversed and reconsideration is requested for the reasons which follow.

The Examiner takes the position that Wieder, et al. discloses all of the limitations of claim 1 except for the specific ranges of light wavelengths of excitation. The Examiner then relies on Kardos, et al. for disclosing the specific ranges of light wavelengths of excitation claimed in claim 1 of the present application. More specifically, the Examiner relies on the disclosure in Wieder, et al. of sensitizing moieties which are similar to those disclosed in the present application as the basis of concluding that Wieder, et al. discloses all of the elements of claim 1 except the specific ranges of light wavelengths.

As Dr. Brunner points out, the lanthanide-ligand complex employed by Wieder et al. is substantially different from the lanthanide-ligand complex employed in the present invention. More specifically, Wieder et al. teaches two separate photoluminescence assay embodiments. The first assay embodiment employs a fluorescent ligand-lanthanide metal complex that uses substituted pyridine or polyamine polycarboxylic acid as the ligand, which absorbs light in the ultraviolet (hereafter "UV") range (< 400 nm).

The ligand used in the first embodiment of Wieder et al does not contain a sensitizing moiety which absorbs light in the 400-1000 nm region. The first assay embodiment employs rhodamines or a fluorescein type material to quench the fluorescence emission from the ligand-

lanthanide metal complex when the rhodamines or fluorescein type material is brought in a distance of about 30.6Å (see col. 9, lines 55-60 of Wieder et al.) to the ligand-lanthanide metal complex via an antibody-analyte binding mechanism. In contrast, the present invention employs a ligand-lanthanide metal complex, wherein the ligand itself contains or is in contact with a sensitizing moiety such as rhodamines or fluorescein. As a result, the distance between the sensitizing moiety and the lanthanide moiety in the ligand-lanthanide metal complex of the present invention is short enough to enable the direct transfer of energy from the sensitizing moiety to the lanthanide metal via a "S-T-M" route. The further discussion with regards to the "S-T-M" route can be found at col. 12, lines 52-56 of Wieder et al. and the declaration of Dr. Brunner.

The second assay embodiment of Wieder et al. employs a fluorescent ligand-lanthanide metal complex that uses substituted pyridine or polyamine polycarboxylic acid as the ligand, which absorbs light in the UV range. The second assay embodiment employs a substituted diphenyloxazole (see col. 13, table 1 of Wieder et al.) to enhance the fluorescence emission from the ligand-lanthanide metal complex when the substituted diphenyloxazole is brought in close proximity (about 50Å, see col. 13, lines 2-5 of Wieder et al.) to the ligand-lanthanide metal complex via an antibody-analyte binding mechanism. The substituted diphenyoxazole also absorbs light in the UV range. The second assay embodiment of Wieder et al. does not employ a material containing rhodamines or fluorescein type moieties. The second assay embodiment of Wieder et al. also does not employ a ligand containing a sensitizing moiety which absorbs light in the 400-1000 nm region.

Accordingly, the structural difference between Wieder et al and the present invention is that the sensitizing moiety employed in the present invention which absorbs in the range of 400-

1000 nanometers is a part of or in contact with the ligand. This is important since the energy transfer between the sensitizing moiety and the lanthanide-ligand complex is distance dependent. Thus, the present invention is optimized for energy transfer whereas in Wieder, et al. the sensitizing moieties relied upon by the Examiner are added to the solution as a separate component and there is a substantial distance (about 30.6 Å, see Brunner's declaration, paragraph 4) between the sensitizing moiety and the lanthanide-ligand complex as pointed out above.

Dr. Brunner, in the enclosed declaration, further points out that the long wavelength organic molecules disclosed in Wieder, et al. such as fluorescein, rhodamine and phycobiliproteins are used to quench the luminescence emitted by the lanthanide-ligand complex of Wieder et al. This is a totally different use than in the present invention and, therefore, Wieder, et al. requires a light wavelength range completely different from the wavelength range which is claimed by independent claims 1, 5, 10 and 12.

Furthermore, a person of ordinary skill in the art would not combine the teachings of Wieder et al. and Kardos et al. Even though Wieder et al. discloses dyes/sensitizing moieties (used as the "quencher") which inherently absorb in the 400-1000 nm range, when the ligand-lanthanide complex of Wieder et al. is irradiated with a 400-1000 nm light source such as is taught in Kardos et al., the ligand-lanthanide complex of Wieder et al. will not emit an IR emission that can be detected by a detector such as that employed in Kardos et al. That is because the dyes/sensitizing moieties cannot transfer their energy to the lanthanide metal complex because of the distance between the dyes/sensitizing moieties and the ligand-lanthanide complex, and the type of ligand-lanthanide metal complex employed in Wieder et al. For example, the lanthanide metal in Wieder et al. predominantly binds with ligands such as

substituted pyridine or polyamine-polycarboxylic acid (see cols. 5 and 6 of Wieder et al.), which do not absorb light in the 400-1000 nm range, and the dyes/sensitizing moieties used in Wieder et al. situate themselves a substantial distance from the lanthanide metal (i.e., about 30.6A, see col. 9, lines 44-49). In fact, the dyes/sensitizing moieties of Wieder et al. which absorb in the 400-1000 nm range are used to quench the emission from the lanthanide metal complex instead of exciting it as would be the case in the present invention. Therefore, the combination of Kardos et al. and Wieder et al. as proposed by the Examiner would not lead to the present invention. Rather, the proposed combination will lead to an inoperable method or apparatus. For these reasons, a person of ordinary skill in the art would not combine the teachings of Wieder et al. with the teaching of Kardos et al. (See paragraph 16 of Dr. Brunner's declaration).

For these reasons it is considered that there are clear differences between the present invention and Wieder, et al. and that the teachings of Wieder, et al. would lead a person of skill in the art to employ wavelengths of excitation below 400 nanometers even if the teachings of Kardos, et al. were considered since the lanthanide-ligand complex suggested by Wieder, et al. cannot be excited at wavelengths above 400 nanometers. See affidavit of Dr. Brunner.

Finally, as mentioned above, Wieder, et al. and Kardos, et al. relate to two totally different systems which cannot be readily combined with one another in the manner that the Examiner suggests.

For the foregoing reasons, favorable consideration and withdrawal of the rejection under 35 U.S.C. §103(a) of claims 1-14 as unpatentable over Weider, et al. in view of Kardos, et al. is respectfully requested.

Respectfully submitted,

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Date: July 12, 2002

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Enclosure:

Rule 132 Declaration from Dr. Brunner

Marked-Up Copy Showing the Claim Amendment

1. (Three Times Amended) A method for detection of an analyte in a test sample comprising the steps of:

preparing a lanthanide ion-ligand complex by mixing a lanthanide ion and a ligand, wherein the lanthanide ion is selected from the group consisting of neodymium (III) ion, ytterbium (III) ion (Yb3+) and erbium (III) ion (Er^{3+}), and wherein said ligand comprises a sensitizing moiety, which absorbs light in the 400 –1000 nm region;

labeling a reactant or ~~n~~ immunoreactant with the lanthanide ion-ligand complex by contacting the reactant or immunoreactant with the lanthanide ion-ligand complex to form a labeled reactant or immunoreactant;

mixing an analyte, a specific binding partner for the analyte, and the labeled reactant or immunoreactant to form a mixture, whereby the analyte will bind with the specific binding partner for the analyte and with the reactant or immunoreactant;

irradiating the mixture with light having a wavelength ranging from 400 nm to 1000 nm; ~~and~~

measuring an emitted luminescence~~ance~~ from said mixture; and

detecting the analyte using said luminescence measurement.

4. (Three Times Amended) The method as claimed in any one of claims 1 and 10, wherein the ligand is a composition which comprises, as one of its constituents, a compound which comprises an element selected from the group consisting of oxygen, nitrogen, phosphorous, and sulfur moieties which ~~have complexing ability towards~~ can complex with Nd

(III), Yb (III), or Er (III) ions, and the sensitizing moiety is selected from [selected from] the group consisting of fluoresce in derivatives; triphenylmethane derivatives; porphyrin derivatives; rhodamine derivatives; phenothiazine derivatives; phenoxazine derivatives; coumarin derivatives; acridin derivatives; thio-indigo derivatives; indigo derivatives; carbocyanine derivatives; squaraine derivatives; ~~and~~ naphthalocyanine derivatives; and phthalocyanine derivatives.

5. (Amended twice) A kit for detection of an analyte in a test sample comprising

a specific binding partner for the analyte;

a reactant or~~n~~ immunoreactant; and

a label wherein the label is a lanthanide ion-ligand complex formed by contacting a lanthanide ion and a ligand, wherein the lanthanide ion is selected from the group consisting of neodymium(III) ion (Nd^{3+}), ytterbium(III) ion (Yb^{3+}), and erbium(III) ion (Er^{3+}), and wherein the ligand comprises a sensitizing moiety which absorbs light in the 400-1000 nm region.

6. (Three Times Amended) An apparatus for detection of an analyte in a test sample comprising:

the kit of claims 5,12, 13 or 14;

a light source in the 400-1000 nm wavelength range; and

a detector, which ~~is capable of detecting~~ detects luminescence in the 800-1600 nm range.

9. (Twice Amended) The apparatus as claimed in claim 6, wherein the detector ~~is capable of detecting~~ can detect luminescence in the 800-1100 ~~nm~~ nm range.

10. (Twice Amended) A method for detection of an analyte in a test sample comprising the steps of:

preparing a lanthanide ion-ligand complex by mixing a lanthanide ion and a ligand, wherein the lanthanide ion is selected from the group consisting of neodymium (III) ion, ytterbium (III) ion (Yb^{3+}) and erbium (III) ion (Er^{3+}), wherein the ligand is in contact with a sensitizing moiety, which absorbs lights in the 400 –1000 nm region;

labeling a reactant or ~~an~~ immunoreactant with said lanthanide ion-ligand complex by contacting the reactant or immunoreactant with the lanthanide ion-ligand complex to form a labeled reactant or immunoreactant.

mixing the analyte, a specific binding partner for the analyte and the labeled reactant or immunoreactant to form a mixture, whereby the analyte will bind with the specific binding partner for the analyte and with the reactant or immunoreactant;

irradiating the mixture with light having a wavelength ranging from 400 nm to 1000 nm; ~~and~~

measuring the emitted luminance from the mixture; and

detecting the analyte using said luminescence measurement.

12. (Amended) A kit for detection of an analyte in a test sample comprising:

a specific binding partner for the analyte;

a reactant or~~n~~ immunoreactant; and

a label wherein the label is a lanthanide ion-ligand complex formed by contacting a lanthanide ion and a ligand, wherein the lanthanide ion is selected from the group consisting of neodymium (III) ion (Nd^{3+}), ytterbium (III) ion (Yb^{3+}), and erbium (III) ion (Er^{3+}), and wherein the ligand is in contact with a sensitizing moiety which absorbs light in the 400-1000 nm region.

13. (Amended) The kit as claimed in claim 5, wherein the specific binding partner and the reactant or immunoreactant are attached to a carrier.

14. (Amended) The kit as claimed in claim 12, wherein the specific binding partner and the reactant or immunoreactant are attached to a carrier.